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Editorial Comment

Adenosine-Thallium Imaging: Faster and Better?*

FRANS J. TH. WACKERS, MD, FACC
New Haven, Connecticut

Dipyridamole-thallium-201 imaging. Since the early 1980s dipyridamole–thallium-201 imaging has become a routine procedure in many nuclear cardiology laboratories (1–4). Patients incapable of exercising on a treadmill or bicycle because of orthopedic, neurologic or peripheral vascular disease can be evaluated effectively for the presence of significant coronary artery disease with the use of dipyridamole-thallium imaging. Extensive clinical experience has shown that this noninvasive procedure is relatively safe (5–7) and provides diagnostic and prognostic information comparable to that derived by exercise thallium imaging (1,2,8–16). Nevertheless, for unclear reasons, intravenous dipyridamole has not as yet been approved for this clinical application by the Food and Drug Administration.

Intravenous dipyridamole causes selective vasodilation of the coronary resistance vasculature. In patients with significant coronary artery disease this results in regional heterogeneity of myocardial blood flow that can be imaged with thallium-201 (17). The vasodilative action of dipyridamole is the *indirect* result of elevation of *endogenous adenosine* levels by blocking reentry of adenosine across the cell membrane (18–20).

Although intravenous dipyridamole-thallium imaging has proved its clinical usefulness, the degree of vasodilation achieved by dipyridamole may vary in individual patients. Homma et al. (21) demonstrated a relatively wide range in serum dipyridamole levels after intravenous administration. Maximal pharmacologic effect occurs approximately 4 min after completion of infusion and is maintained for approximately 20 to 40 min. This relatively prolonged effect poses a potential problem in patients who experience adverse reactions. Usually these side effects can be reversed readily by intravenous aminophyline (22,23); however, because of the prolonged effect of dipyridamole, at times symptoms may recur after an initial favorable response.

Adenosine-thallium-201 imaging. Because of the limited availability of dipyridamole for this application (one needs a physician's Investigational New Drug number issued by the Food and Drug Administration), alternative pharmacologic approaches to achieve coronary vasodilation, such as the use of papaverine or nitroglycerin, have been explored. Recently, intravenous infusion of adenosine has been proposed as a means of achieving *directly* what is an *indirect* effect of dipyridamole (24). Adenosine is a potent fast-acting endogenous coronary vasodilator that relaxes vascular smooth muscle by either inhibition of the slow inward calcium current or activation of adenylate cyclase (25). It is quickly metabolized in red blood cells, which accounts for its short half-life.

Two particularly attractive aspects of adenosine for clinical pharmacologic vasodilation are its rapid onset of action and extremely short half-life. Wilson et al. (26) demonstrated a near (4.5 times) maximal increase in coronary blood flow at 120 s after the start of infusion of adenosine. Coronary flow returned rapidly to baseline at 113 s after termination of the infusion. In contrast, with the use of dipyridamole the increase of myocardial blood flow occurs more gradually, is generally less in magnitude and is more variable. Maximal increase in coronary blood flow is not achieved in all patients (27).

The present study. In this issue of the Journal, Nguyen et al. (28) report on the feasibility, safety and diagnostic accuracy of adenosine-thallium single photon emission computed tomographic (SPECT) imaging. Although the number of patients studied was relatively small (53 patients with and 7 patients without coronary artery disease), the diagnostic accuracy of adenosine-thallium imaging was comparable to that of exercise thallium imaging. Of particular interest are the observations in the subgroup of patients who also had two-dimensional echocardiography. During adenosine infusion only 2 of these patients had echocardiographic regional wall motion abnormalities, whereas 16 of 20 patients had reversible thallium perfusion defects. Assuming that adenosine achieved maximal coronary vasodilation, these observations can be compared with those of Picano et al. (29), who performed high dose dipyridamole echocardiography. The observations of Nguyen et al. (28) indicate that thallium-201 perfusion abnormalities occur more frequently and may occur without associated echocardiographic regional wall motion abnormalities. These findings imply that adenosine-induced heterogeneity of blood flow often does *not* result in myocardial ischemia.

The results of Nguyen et al. (28) are comparable with those published recently by Verani et al. (30). Employing

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From the Cardiovascular Nuclear Imaging and Exercise Laboratories, Departments of Medicine (Cardiology) and Diagnostic Radiology (Nuclear Medicine), Yale University School of Medicine, New Haven, Connecticut.

Address for reprints: Frans J. Th. Wackers, MD, FACC, Yale University School of Medicine, Cardiovascular Nuclear Imaging Laboratory, 333 Cedar Street, TE-2 New Haven, Connecticut 06510.

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Table 1. Reported Side Effects (% of patients) of Intravenous Dipyridamole- and Adenosine-Thallium Imaging

	Dipyridamole	Adenosine	
	Rankosky et al. (7)	Verani et al. (30)	Nguyen et al. (28)
Cardiac			
Fatal MI	0.05	0	0
Nonfatal MI	0.05	0	0
Chest pain	19.7	57	38
ST-T changes on ECG	7.5	12	12
Ventricular arrhythmia	5.2	—	—
Tachycardia	3.2	—	—
Hypotension	4.6	—	—
Blood pressure lability	1.6	—	—
Hypertension	1.5	—	—
AV block	0	10	13
Noncardiac			
Headache	12.2	35	20
Dizziness	11.8	—	8
Nausea	4.6	—	8
Flushing	3.4	29	58
Pain (nonspecific)	2.6	—	—
Dyspnea	2.6	15	13
Paresthesia	1.3	—	—
Fatigue	1.2	—	—
Dyspepsia	1.0	—	—
Acute bronchospasm	0.15	0*	0*

*Patients with history of bronchospasm excluded. AV = atrioventricular; ECG = electrocardiogram; MI = myocardial infarction.

incremental infusion doses of adenosine and thallium-201 SPECT imaging, the latter investigators reported an overall sensitivity of 83% and a specificity of 94% for detecting angiographic coronary artery disease in 57 patients.

Both the study of Verani et al. (30) and that of Nguyen et al. (28) report a relatively high incidence of side effects: 88% and 83%, respectively. In general, these adverse reactions were reported to be mild and were usually resolved within 1 to 2 min after termination of adenosine infusion. In comparison, the reported incidence of side effects of 35% with dipyridamole infusion is considerably lower. In particular, chest, throat or jaw pain occurred more frequently with the administration of adenosine than of dipyridamole (Table 1). An adverse effect that has attracted much attention and has raised considerable concern is the occasional occurrence of high degree atrioventricular block. However, this complication is infrequent and is resolved promptly after discontinuation of adenosine infusion. No patients in the current study needed placement of a temporary pacemaker.

Adenosine versus dipyridamole-thallium imaging. Adenosine-infusion is an attractive alternative for pharmacologic vasodilation in combination with thallium-201 imaging because of its fast onset of action, near maximal coronary vasodilation and short half-life. These favorable characteristics may allow a more consistent pharmacologic effect in all patients than is achieved with dipyridamole.

The diagnostic and prognostic significance of abnormal dipyridamole-thallium studies has been well documented (11–16,31). There is no reason to believe that adenosine–thallium-201 imaging would be any less effective. The recent reported results (28,30) are extremely promising. The relatively high incidence of side effects is of concern and should be evaluated in a larger number of patients with a broader range of clinical presentations of coronary disease. The short half-life makes it possible to quickly adjust the dose of adenosine infusion and control potentially serious adverse reactions. Further clinical experience should also clarify whether the two compounds can be employed interchangeably or whether in certain patient groups one is preferred over the other.

Combination with newer imaging agents. Adenosine may be particularly suited for use with the recently developed new technetium-99m–labeled myocardial perfusion imaging agents. For instance, technetium-99m teboroxime is a myocardial perfusion imaging agent with markedly different characteristics from those of thallium-201. After initial accumulation according to the distribution of myocardial blood flow, it is cleared from the heart within 3 to 4 min (32). Adenosine infusion would allow appropriate timing of injection of technetium-99m teboroxime at maximal coronary vasodilation. Furthermore, the short half-life of adenosine, as well as the rapid clearance of technetium-99m teboroxime, would make it possible to perform repeat studies within a short time.

In contrast, another new imaging agent, technetium-99m methoxy-isobutyl isonitrile (SestaMIBI), remains "fixed" in the heart for a number of hours after initial distribution according to myocardial blood flow (33). Imaging usually is performed 40 to 60 min after injection. Repeat imaging can be performed several hours later or on a different day. Neither dipyridamole nor adenosine would seem preferable to this new agent.

Conclusions. Pharmacologic vasodilation–myocardial perfusion imaging has become an important and useful alternative to exercise testing. It is to be hoped that the accumulated evidence of clinical safety may prompt the Food and Drug Administration to approve these compounds for this application in the very near future.

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